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- (74) Agents: LEVY, David, J et al.; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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 without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CCR5 ANTAGONISTS AS THERAPEUTIC AGENTS

(57) Abstract: The present invention relates to compounds of formula (I) or pharmaceutically acceptable derivatives thereof, useful in the treatment or prophylaxis of CCR5-related diseases and disorders, for example, in the inhibition of HIV replication, the prevention or treatment of an HIV infection, and in the treatment of the resulting acquired immune deficiency syndrome (AIDS).

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A61K 31/46,

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- (84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

#### Published:

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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 2 September 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIPERIDINE DERIVATIVES AS CCR5 ANTAGONISTS

$$R^3 - (Y)_{\overline{m}} N \times X^2 - (R^2)_n$$
(I)

(57) Abstract: The present invention relates to compounds of formula (I) or pharmaceutically acceptable derivatives thereof, useful in the treatment or prophylaxis of CCR5-related diseases and disorders, for example, in the inhibition of HIV replication, the prevention or treatment of an HIV infection, and in the treatment of the resulting acquired immune deficiency syndrome (AIDS).

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/46 A61K31/445 C07D451/04 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

#### **B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  $IPC \ 7 \ CO7D$ 

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

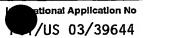
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Υ	WO 99/04794 A (OATES BRYAN; FINKE PAUL E (US); MACCOSS MALCOLM (US); MERCK & CO INC) 4 February 1999 (1999-02-04) page 103, line 12 - line 17; claims 1,15,18,20	1-61
Υ	WO 00/38680 A (EDWARDS MARTIN PAUL; PRICE DAVID ANTHONY (GB); PFIZER LTD (GB); WOOD) 6 July 2000 (2000-07-06) page 27, line 10; claims 1,2,5-20	1-61
A	WO 02/079190 A (COOPER DAVID GWYN; FORBES IAN THOMSON (GB); GRIBBLE ANDREW DERRICK (G) 10 October 2002 (2002-10-10) page 12, line 1 - line 3; claim 1; table 1	1-61

X Further documents are listed in the continuation of box C.	Y Patent family members are listed in annex.
Special categories of cited documents:  A* document defining the general state of the art which is not considered to be of particular relevance  E* earlier document but published on or after the international filling date  L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  O* document referring to an oral disclosure, use, exhibition or other means  P* document published prior to the international filling date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  "&" document member of the same patent family
Date of the actual completion of the International search  4 June 2004	Date of mailing of the international search report  2 5, 06. 04
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentiaan 2  NL – 2280 HV Rijswijk  Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,  Fax: (+31–70) 340–3016	Authorized officer Seymour, L





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C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Х	WO 98/25605 A (SPRINGER MARTIN S; MACCOSS MALCOLM (US); MERCK & CO INC (US); MILLS S) 18 June 1998 (1998-06-18) page 61, line 5 - line 11; claims 1,11 page 16 - page 34	1-61
X	US 5 340 822 A (EMONDS-ALT XAVIER ET AL) 23 August 1994 (1994-08-23)	1-23, 25-28, 52-54, 59,60
	column 1, line 11 - line 24; claim 1; examples 22-24	
X	BE 601 228 A (JANSSEN PHARMACEUTICA) 1961	1-23, 25-28,54
	page 2, line 23 - line 27; claim 1 page 9, line 10 - page 28, line 10	
X	US 2 773 870 A (BILL ELPERN) 11 December 1956 (1956-12-11) column 1, line 20 - line 61 examples	1-23, 25-28,54
X	US 3 539 580 A (HERMANS HUBERT KAREL FRANS ET AL) 10 November 1970 (1970-11-10) column 1, line 13 - line 15; claims 1,5-7 table	1-23, 25-28,54
X	US 3 334 106 A (BIEL JOHN H) 1 August 1967 (1967-08-01) the whole document	1-23, 25-28,54
X	REHSE K ET AL: "Platelet aggregation inhibiting and anticoagulant effects of oligoamines, 1: N-(4-piperidinyl)methanamines" ARCHIV DER PHARMAZIE, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, DE, vol. 319, no. 319, 1986, pages 505-515, XP001085385 ISSN: 0365-6233 the whole document	1,25-28, 52-54, 59,60
X	STEVENTON ET AL: "4,4-disubstituted Piperidine High-Affinity NK1 Antagonists: Structure-Activity Relationships and in Vivo Activity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 41, no. 23, 1998, pages 4623-4622, XP002173109 ISSN: 0022-2623 the whole document	1,25-28, 54

# INTERNATIONAL SEARCH REPORT

		US 03/39644
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 248 018 A (OTTO EISLEB) 1 July 1941 (1941-07-01) column 1, line 52 - line 55; claim 6; examples 3,4	1,25-28, 54
X	WO 98/25604 A (SPRINGER MARTIN S; MACCOSS MALCOLM (US); MERCK & CO INC (US); MILLS S) 18 June 1998 (1998-06-18) page 30, line 26 - line 30 page 34, line 1 - line 22 page 55 - page 85; claim 1	1,7-12, 20,25-61
X	DATABASE WPI Section Ch, Week 200335 Derwent Publications Ltd., London, GB; Class B02, AN 2003-367209 XP002283279 -& JP 2002 348288 A (ONO PHARM CO LTD) 4 December 2002 (2002-12-04) abstract	1,7-12, 20,25-61



Box t	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This inte	rnational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. χ	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
	Although claims 42-53 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. X	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: see FURTHER INFORMATION sheet PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	ernational Searching Authority found multiple inventions in this International application, as follows:
	see additional sheet
1. X	As all required additional search fees were timely paid by the applicant, this international Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark	The additional search fees were accompanied by the applicant's protest.  X No protest accompanied the payment of additional search fees.
	•

# FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 42-53 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.:

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds according to claim 3 for invention 1. For invention 2, a selection of novelty-destroying documents disclosing spiro fused CCR5 modulators have been cited.

In addition, the present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The term "pharmaceutically acceptable derivative" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include "pharmaceutically acceptable derivatives" of the compounds of formula I.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

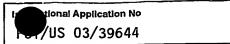
# INTERNATIONAL SEARCH REPORT

mation on patent family members

I ational Application No
/US 03/39644

					/US	03/39644
Patent docume cited in search re		Publication date		Patent family member(s)		Publication date
WO 9904794	A	04-02-1999	AU	8576098	Α	16-02-1999
			CA	2296314		04-02-1999
			EP	1003514		31-05-2000
			JP	2002510327		02-04-2002
			WO	9904794		04-02-1999
			US	6136827		24-10-2000
WO 0038680	Α	06-07-2000	AU	769449		29-01-2004
			AU	1290400		31-07-2000
			AU	763644		31-07-2003
			AU	1675100		31-07-2000
			BG	105709		28-02-2002
			BG	105721		28-02-2002
			BR	9905977		14-01-2003
			BR	9916585		16-10-2001
			BR CA	9917007 2292984		30-10-2001
			CA	2292984 2350073		23-06-2000 06-07-2000
			CA	2350573		06-07-2000
			CN	1331691		16-01-2002
			CN	1331591		16-01-2002
			CZ	20012297		11-09-2002
			CZ	20012298		11-09-2002
			EE	200100344		15-10-2002
			ĒĒ	200100345		16-12-2002
			ĒΡ	1013276		28-06-2000
			ĒΡ	1140920		10-10-2001
			ĒΡ	1140085		10-10-2001
			HR	20010468		28-02-2003
			HR	20010478		30-06-2002
			HU	0104795		29-04-2002
			HU	0104910	A2	28-10-2002
			WO	0039125	A1	06-07-2000
			WO	0038680		06-07-2000
			ID	29031		26-07-2001
			ID	28965		19-07-2001
			JP	2000212159		02-08-2000
			JP	2002533393		08-10-2002
			JP	3522691		26-04-2004
			JP	2002533461		08-10-2002
			JP	2004099618		02-04-2004
			NO	20013149		23-08-2001
			NO NZ	20013183		08-08-2001
			NZ	511794		31-10-2003
			NZ	511796		28-11-2003
			PL	349091		01-07-2002
			PL SK	349495 8752001		29-07-2002
			SK	8752001 8762001		04-02-2003
			TR	200101793		04-02-2003 21-12-2001
			TR	200101793		21-12-2001 21-11-2001
			TR	200101867		21-11-2001 21-05-2002
			US	6586430		01-07-2003
						14-01-2002
			ZA	200104211	. ^	14 01 2002
 WO 0207919	0 A	10-10-2002	WO	02079190		10-10-2002

#### TIONAL SEARCH REPORT INTER mation on patent family members



Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9825605	A		WO US	9825605 5962462		18-06-1998 05-10-1999
US 5340822	Α	23-08-1994	 FR	2676055		06-11-1992
US 53400ZZ	^	23-00-1994	AT	181550		15-07-1999
			AU	652046		11-08-1994
			AU	1591692		05-11-1992
			BR	9201656		15-12-1992
			CA	2067877		04-11-1992
			CS	9201329		18-11-1992
			DE	69229460		29-07-1999
			DE	69229460		20-01-2000
			DK	51290		06-12-1999
			EP ES	0512901 2137176		11-11-1992 16-12-1999
			FI	92195		04-11-1992
			FI	951242		16-03-1995
			ΓĪ	951243		16-03-1995
			GR	303075		30-11-1999
			HK	1005138		12-05-2000
			HU	61539	9 A2	28-01-1993
			ΙE	92136		04-11-1992
			IL	10176		18-02-1997
		•	IL	11792		18-02-1997
			JP	324298		25-12-2001
			JP	518642		27-07-1993
			KR MV	258373 9202023		01-07-2000 01-01-1993
			MX NO	920202		01-01-1993
			NZ NZ	24258		26-10-1995
			RU	208357		10-07-1997
			ÜS	577073		23-06-1998
			US	562506	0 A	29-04-1997
			ZA	920317	8 A 	27-01-1993
BE 601228	A		NONE			
US 2773870	Α	11-12-1956	NONE			
US 3539580	Α	10-11-1970	BE	71714		27-12-1968
			CH	48572		15-02-1970
			DE	177060		04-11-1971
			ES	35490		16-11-1969
			FR FR	745 156947	3 M	24-11-1969 30-05-1969
			F K GB	119936		22-07-1970
			NL	680841		27-12-1968
US 3334106	A	01-08-1967	NONE			
US 2248018	Α	01-07-1941	NONE			
WO 9825604	Α	18-06-1998	AU	560499	8 A	03-07-1998
			WO	982560		18-06-1998
			US	601366	4 A	11-01-2000
JP 2002348288	Α	04-12-2002	NONE			